In re Appln. of SMIT et al.
Application No. 08/807,506

REMARKS

Reconsideration and allowance are respectfully requested.

Petition for Extension of Time

Applicants are a small entity and respectfully petition for a three month extension of time to even date herewith. The petition fee can be charged to deposit account 06-1135 regarding order number 7392/71226.

Amendments

Applicants acknowledge the Examiner's invitation to amend the specification to update the lineage for purposes of 35 U.S.C. §120. The cover sheets to the March 14, 2000 CPA would seem adequate inasmuch as the then rule not requiring recitation of CPA status is cited. It would seem that such rule would be equally germane to the July 13, 2001 CPA, and to the April 2, 2002 CPA (re-designated RCE). If the Examiner would prefer that Applicants undertake to amend their specification, please contact the undersigned so that suitable language can be considered and introduced as appropriate.

Applicants have amended the claims and endeavored to adapt, where appropriate, the Examiner's constructive suggestions regarding matters of form. It is noted that although claim 119 has been amended by replacing "almost" with 'about' the former claim satisfied formality requirements inasmuch as US patents have issued with "almost" appearing in their claims. There is no intention to narrow the claim scope.

The Application Satisfies 35 U.S.C. §112(¶¶ 1 and 2).

Applicants respectfully suggest their claims satisfy 35 U.S.C. §112(¶2).

Applicants respectfully suggest their claims satisfy 35 U.S.C. §112(¶1). Claims 94-132 find basis in a specification that satisfies with the enabling written description requirement. As described to those skilled in the art, the chemical modifications disclosed are dramatic and both their effectiveness and location in the molecule(s) being modified is readily ascertained in a convenient manner. The specification discloses and exemplifies gradual chemical modification, such as with anhydrides (acetic and succinic anhydrides),

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with iodo acetate and enzymatic treatments. For instance, as to claims 94-132, and particularly claims 125-127, literature confirms the inventions and attention may be directed, for instance, to Subbramanian et al., J. Clin. Microbiol. 40(6):2141-6.

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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CLAIMS AS AMENDED

Please amend and/or add claims:

94. (Amended) A method for quantitative structure function analysis research on biologically active proteins or peptides, said method comprising applying a specific chemical modification of selected amino acids **to said proteins or said peptides whereby said modification results in said proteins and peptides having** [to introduce] at least one feature selected from the group consisting of enhanced biological activity, enhanced stability, suppressed antigenicity, acquired antagonistic activity, and cell inhibitory activity [is introduced into said proteins or peptides], said method comprising:

a) gradual chemical modification of a protein or peptide, followed by

b) monitoring the modification reaction with a mild and sensitive method such as nondenaturing electrophoresis or electrospray mass spectrometry and optionally confirming the overall structural integrity;

c) protease treatment;

d) mass spectrometry;

e) assaying biological activity of the modified product and optionally assaying stability of the modified protein.

100. (Amended) The method according to claim 94 or 99, wherein specific digestion with specific endoproteases and **laser desorption mass spectometry** [LDMS] is carried out for **characterization** [charcterisation] and **localization** [localisation] of the modified amino acids.

104. (Amended) The method according to claim 94 or 99, wherein [the modification is] **said** chemical modification [, said modification] **comprises** [being] alkylation or [said modification being] acylation,[such as e.g. by Iodo acetate or succinylation, e.g. by succinic anhydride,] said **chemical** modification [suitably being conducted under gradually varying conditions, wherein one or more of the following conditions are varied as follows:] **being conducted while gradually varying at least on of the conditions under which said**

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modification is conducted, said conditions comprising a pH **in a range between a pH of** 5.0 and 7.0, [preferably in steps of 0.5 pH units, and/or] **the** time **for conducting said modification, and** [or] reagent[-] concentrations [are varied],

107. (Amended) The method according to claim 94 or 99, wherein the modification is within or in a **such** close proximity to a metal binding center **that it effects a feature selected from the group consisting of biological and chemical features**[, preferably a Zinc binding center, suitably said residue is a histadine residue].

108. (Amended) The method according to claim 94 or 99, wherein the modification is performed by reversibly denaturing the substrate and adding chelating agent to remove the metal ion, **said chelating being conducted** [e.g.] in the presence of urea and EDTA[, said urea preferably having a concentration larger than 5M and said EDTA preferably having a concentration of 50 mM.].

109. (Amended) The method according to claim 94 or 99, wherein the modification is specific for one type of amino acid[, for instance an amine-residue and/]or even is specific for only 1 amine-residue in the peptide or protein[, said 1 amine for instance being the N-terminus].

111. (Amended) The method according to claim 94 or 99, **wherein said chemical modification comprises disruption of phosphate binding whereby the modification results in said proteins or peptides having** [for the introduction] **at least one of** an antagonisitc [and/]or cell inhibitory activity[, said method comprising disruption of phosphate binding].

112. (Amended) A modified signal substance selected from the group consisting of a protein hormone, peptide hormone, growth factor, a haemopoeitic growth factor, an inteferon, an interleukin and a colony stimulating factor with enhanced biological activity, antagonistic activity or cell inhibitory activity, wherein said signal substance contains a modification within or in **such** close proximity to a catalytic center **that it results in a**

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biological or biochemical feature[, preferably such that the catalytic activity is changed, said modification further preferably being within or in close proximity to a metal binding center].

113. (Amended) A modified signal substance being a Zinc binding signal peptide[, preferably] selected from Growth Hormone, prolactin, [and] insulin, **and a member of** the same (cytokine) superfamily as the IL-3 receptor, [preferably IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, GM-CSF, Epo, IFN-gamma, more preferably selected from the following: IL-2, IL-3, IL-6, IFN-gamma, Growth Hormone, prolactin and insulin,] said modified substance having an enhanced biological activity, antagonisitc activity [and/]or cell inhibitory activity, wherein the modification is [preferably] within or in such close proximity to a Zinc binding center[, such] that the metal binding properties have been changed.

114. (Amended) The substance according to claim 113, wherein the metal ion is within or in such close proximity to a catalytic center that it effects a biological or biochemical feature[, preferably said metal ion having a catalytic function in the unmodified substance].

115. (Amended) The substance according to one of claims 112-114, wherein the modification for producing an antagonist is a chemical modification[, preferably] **comprising** an alkylation, an acylation or molecular biological modification, **wherein said molecular biological modification includes** [like] a deletion mutation [and/] or substitution mutuation.

119 (Amended) The substance according to claim 118, comprising at least one of the following characteristics

a) 0.1 ng of the substance, modified IL-3 inhibits [almost] **about** 50% of 3ng/ml native IL-3;

b) 3 ng/ml of the substance, modified IL-3 suppresses 80-90% thymidine incorporation of 30-100 ng/ml control IL-3;

c) the substance modified IL-3 inhibits control IL-3 by a factor of 10-100.

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122. (Amended) A method for preparing a substance according to one of claims 112-114, said method comprising by applying a specific chemical modification of selected amino acids to **a signal substance whereby said modification results in said signal substance having** [introduce] at least one feature selected from the group consisting of enhanced biological activity, enhanced stability, suppressed antigenicity, acquired antagonistic activity, and cell inhibitory activity [is introduced into said proteins or peptides], said method comprising the steps of

a) gradual chemical modification of the signal substance, followed by

b) monitoring the modification reaction with a mild and sensitive method such as nondenaturing electrophoresis or electrospray mass spectrometry and optionally confirming the overall structural integrity;

c) protease treatment;

d) mass spectrometry;

e) assaying biological activity of the modified product and optionally assaying stability of the modified signal substance.

123. (Amended) The substance according to one of claims 112-114, wherein the concentration of substance required for [significant] inhibition is suitable for clinical application, being less than a hundred fold higher than the native substance concentration, said substance optionally further having increased receptor binding capacity.

125. (Amended) A method of obtaining at least inhibition or suppression of a HIV infection wherein the antibody levels are lowered by any of the following steps

a) suppression of antibody production by B-cells, suppression of generation [and/]or maturation of B-cells, preferably said B-cells being anti-HIV-antibody producing B-cells, preferably anti-HIV coat-antibody producing B-cells;

b) plasmaphoresis, partial or complete plasma recovery or selective return of serum,

c) *in vitro* removal of antibodies, preferably HIV-reactive antibodies, preferably HIV-envelope reactive antibodie;

d) *in vivo* depletion, preferably with antibodies, preferably against HIV, preferably against the HIV envelope; **or**

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e) leukophoresis.

126. (Amended) The [substance] **method** according to claim 125, **wherein said method involves** [comprising] application of a preparation that is a modified signal substance or

a modified [signal substance being] a zinc binding signal peptide[, wherein said modified signal substance comprises interleukin 3].

127. (Amended) The method according to claim 125, **wherein said method comprises** [comprising] application of bi-specific antibodies, [preferably] **said antibodies optionally** being directed against **at least one of** the combinations CD19/CD3 [and/]or CD20/CD3.

128. (Amended) The method according to claim 125, **wherein said method comprises** [comprising] application of B-cell apoptose inducing substances[, preferably APO-1 and/]or application of TGF-β as inhibitor of B-cell antibody production.

129. (Amended) A method for stimulating stem cell-replication comprising application of a preparation that is a modified signal substance or a modified signal substance being a zinc binding signal peptide, wherein said modified signal substance comprises interleukin 3 [and/]or a substance obtainable according to [any of the method steps according to] claim 94.

132. (Amended) A method for stimulating stem cell-replication comprising application of a substance obtainable according to [any of] the method [steps] of claim 94.

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